Research uncovers how to target 'sleeping' breast cancer cells and prevent relapse

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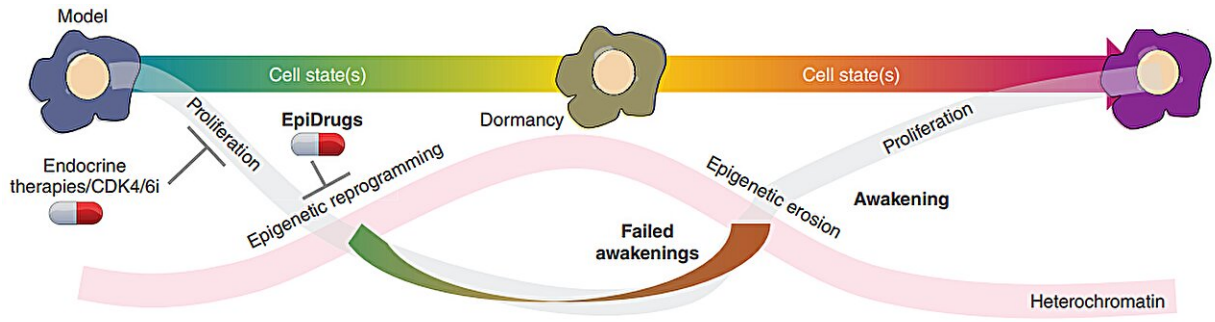

Model: Endocrine therapy-induced dormancy is characterized by a consistent epigenetic reprogramming involving a global increase in histone repressive marks. The dormant epigenome is unstable and through a progressive loss of the histone repressive marks (erosion), cells resume proliferation in a process that mimics patient relapse (awakening). Credit: *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-1161

Scientists have discovered how breast cancer cells can "hibernate" to avoid treatment and "wake up" years later—causing a relapse that is more difficult to treat.

Their research, published in the journal *Cancer Discovery*, reveals the role of epigenetics in controlling how cancer cells can become dormant—and suggests a strategy to target it before the cells wake up.

Epigenetic changes alter how your body reads your DNA, without changing the DNA code itself.

Patients with estrogen receptor positive (ER^+) breast cancer—which make up 80% of all breast cancers—have a continued risk of their cancer recurring for many years or even decades after their original diagnosis and surgery. To reduce their risk of relapse, patients undergo five to 10 years of hormone therapy to target any remaining cancer cells.

The epigenetic mechanism

The team at The Institute of Cancer Research, London, found that this hormone therapy—to reduce the risk of cancer returning—could in some cases play a role in triggering epigenetic changes that alter the state of some breast cancer cells, causing them to become dormant and evade treatment.

The team discovered that specific changes in key epigenetic regulators that control gene transcription, including the modification of histone H3 at lysine 9 (H3K9me2), were responsible for this dormant state. These changes remain until the cell "wakes up" and begins dividing rapidly again.

The scientists worked on the study in the Breast Cancer Now Toby Robins Research Center at The Institute of Cancer Research (ICR), having started the research at Imperial College London.

They found, in the lab, that blocking these regulators—by inhibiting the enzymes that catalyze them—prevented the cells from becoming dormant, and killed the cancer cells that were already dormant. They also found that in people with low expression of these enzymes, their cancer had a lower risk of coming back years later.

The role of H3K9me2

The team studied ER^+ breast cancer cells that they tagged with unique barcodes—an innovative way to study millions of cells through space and time.

They mimicked hormone therapy treatment on the cells and saw that while most cells died, others became dormant and stopped proliferating.

Using mass spectrometry, the team discovered that hormone therapy treatment triggered changes to histone modifications including H3K9me2 as the cells went into dormancy.

Histone modifications are chemical tags that are added to or removed from DNA, or the proteins DNA is wrapped around. Epigenetic modifications such as this are chemical changes to the three-dimensional structure of DNA, which don't alter the DNA code itself but can control access to genes.

Targeting G9a could prevent breast cancer relapse

The researchers set out to uncover whether blocking these epigenetic changes could prevent the cells from becoming dormant and evading treatment. To do this, they inhibited the enzyme G9a, which catalyzes H3K9me2.

The researchers first tested this on cells which had just been treated with hormone therapy and found that it prevented the cancer cells from entering dormancy—in fact, it killed the cells.

Then, they tested it on cells which were already in a dormant state and found that inhibiting G9a killed dormant cancer cells.

To understand the importance of G9a in people, the researchers studied a cohort of patients with ER^+ breast cancer. They found that for those who had low expression of enzymes such as G9a, their breast cancer had a significantly lower risk of relapse over the course of 15—20 years.

Professor Luca Magnani, Professor of Epigenetic Plasticity at The Institute of Cancer Research, London, said, "After surgery to remove primary estrogen receptor positive breast cancer, patients are given five to 10 years of hormone therapy which aims to kill any remaining cancer cells. We know that this doesn't work for all patients though, as their breast cancer can return years, or even decades later. We wanted to better understand why breast cancer does return so we can hopefully find ways to stop it—so people don't have to live in fear or face the devastating news of a relapse.

"Our research identified a key mechanism used by cancer cells to evade therapy by remaining in a dormant state, hibernating before they 'wake up' years later and begin to rapidly divide again. I hope our early findings will next lead to research to target these dormant breast cancer cells so that one day, without the need for years of hormone therapy, patients can be sure that their cancer will not return."

Professor Kristian Helin, Chief Executive of The Institute of Cancer Research, London, and a leading researcher of epigenetics and cancer, said, "This research adds to the growing body of evidence for the role of epigenetic regulation in cancer's complex behavior.

"We know that cancer will adapt and evolve to evade treatment, and this study shows how it will lie dormant to hide from treatment. Drugs targeting epigenetic modifications are already in development, and I hope that this research will pave the way to new treatments that prevent breast cancer from returning."

Dr. Tayyaba Jiwani, Science Engagement Manager at Cancer Research UK, stated, "Breast cancer survival has doubled in the U.K. over the last 50 years thanks to better detection and screening, but there are still more than 11,000 deaths from this type of cancer every year.

"Our research has made it increasingly clear that cancer cells can lie dormant in the body for many years before being triggered to reawaken, causing cancer to return. This study uses an innovative approach to analyze the genetics of these dormant cells and gain important insight into the mechanisms leading to dormancy.

"Although at an early stage, the findings reveal potential new targets for the development of innovative treatments that prevent breast cancer from coming back."

More information: Dalia Rosano et al, Long-term Multimodal Recording Reveals Epigenetic Adaptation Routes in Dormant Breast Cancer Cells, *Cancer Discovery* (2024). DOI: 10.1158/2159-8290.CD-23-1161

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